21. (Twice Amended) An immobilized nucleic acid comprising a nucleic acid linked via a covalent bond to a carrier macromolecule having a molecular weight in excess of 80,000, which macromolecule is bound to a solid support.

22. (Twice Amended) A method of using the immobilized nucleic acid as claimed in claim 21 comprising:

formulating the immobilized nucleic acid as a primer or as a hybridization probe and

introducing the immobilized nucleic acid into a hybridization or amplification reaction utilizing a primer or a hybridization probe.

II. REMARKS

Preliminary Remarks

This response is timely filed as it is accompanied by a petition for an extension of time to file in the third month and the requisite fee. In view of the fact that a request for continued examination is being filed herewith, the applicant requests entry of the foregoing amendment and reconsideration and allowance of the pending claims.

In Paragraph 2 of the final official action, the examiner objected to improper multiple dependencies with respect to claims 7-9, 11-13, 15, and 16. In response, the applicant submits that this objection is now moot. Specifically, by the foregoing amendment, the applicant has removed all improper multiple dependencies. Therefore, the applicant requests the withdrawal of the objection under 37 C.F.R. §1.75(c).

Claims 1-22 are pending in the instant application. Claims 1, 4-8, 10, 12, 15, 16, 18, 21, and 22 have been amended to more clearly define the applicant's invention. Support for

the language "having a molecular weight in excess of 80,000" may be found at page 9 of the specification as originally filed. No new matter is believed to have been introduced herein.

The examiner rejected claims 1-20 under the judicially-created doctrine of obvious-type double patenting in view of claims 1-15 of U.S. Patent No. 6,207,385. In view of the terminal disclaimer disclosed herein, the applicant requests withdrawal of this rejection.

As a convenience to the examiner, the applicant has enclosed herewith, as an appendix, a marked-up version of the claims to show changes made.

Patentability Remarks

35 U.S.C. §112, First Paragraph

The examiner rejected claim 1-22 under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that, at the time the application was filed, the inventors were in possession of the claimed invention. Specifically, the examiner alleged that the language "a carrier macromolecule that does not inhibit DNA polymerase activity" is not supported by the specification.

The applicant submits that this rejection is now moot. In order to expedite prosecution and without prejudice to the applicant's right to seek similar claims in a duly filed continuing application, the applicant has removed such language from claims 1, 18, and 21. Therefore, the applicant requests the withdrawal of this rejection based upon 35 U.S.C. §112, first paragraph.

35 U.S.C, §102(b)-35 U.S.C. §103(a)

Claim 21 was rejected under 35 U.S.C. §102(a) as allegedly being anticipated by or in the alternative under 35 U.S.C. §102(a) as allegedly being obvious over U.S. Patent No. 5,814,445 (hereinafter the '445 patent). It is the examiner position that although the '445 patent did not directly show that the macromolecule (glycogen) was bound to a solid support, the absence of convincing evidence to the contrary, the limitation was considered to be inherent to the '445 patent, since it was known that a complex of the DNA fragment and glycogen was pelleted on the bottom of a centrifuge tube (considered as a solid support) during the precipitation process.

The applicant traverses and submits that the '445 patent does not teach or suggest an immobilized nucleic acid comprising a nucleic acid bound to a carrier macromolecule having a molecular weight in excess of 80,000, which macromolecule is bound to a solid support (see claim 21).

Once again, the applicant respectfully points out to the examiner that the examiner's analysis of the '445 patent is technically inaccurate and misconstrues the facial meaning of the claims. Fundamentally, the '445 patent provides for a process in which glycogen is absent during PCR steps. The '445 patent (at column 8) teaches the ethanol precipitation of DNA from solution using 96 percent ethanol and glycogen as a "carrier." Glycogen is employed in this process step to produce steric exclusion of DNA in order to facilitate precipitation by increasing the effective concentration of the DNA in solution in the presence of an organic solvent. Contrary to the examiner's assertions, DNA is not bound to glycogen, and there is no teaching that DNA bound to glycogen is subjected to PCR amplification.

Claim 21 is directed to an immobilized nucleic acid comprising nucleic acid bound to a carrier macromolecule having a molecular weight in excess of 80,000, the carrier macromolecule itself being bound to a solid support. The examiner admits that the '445 patent did not directly show that glycogen (macromolecule) was bound to a solid support as recited in claim 21." The examiner asserted that the '445 patent inherently teaches bonding to a "solid support" insofar as DNA fragments and glycogen were known to be pelleted onto the bottom of a centrifuge tube.

The applicant finds no support in the '445 patent for such allegations. First, the applicant respectfully points out that there is no disclosure in the '445 patent of the use of a centrifuge tube. Secondly, the applicant respectfully points out to the examiner that one of

skill in the art would readily recognize that physically pelleting DNA and glycogen in a glass tube is not a process of bonding to a "solid support." To the contrary, centrifuge tubes are generally designed to be inert to avoid bonding to the materials introduced to the tubes. The examiner is again invited to explain how the pelleted material of the '445 patent would react with a glass centrifuge tube to form a bond, and to explain where the cited reference teaches this step. Moreover, the '445 patent fails to teach nucleic acid bound to a carrier macromolecule, as the DNA of this reference is not bound to glycogen. Glycogen is employed in this process step to produce steric exclusion of DNA, thereby reducing the "space" in which the nucleic acid may remain in solution. Glycogen, therefore, facilitates precipitation without bonding with the DNA. Indeed, this lack of bonding to glycogen is essential to the process described in the '445 patent because it is necessary to go on to extend the 3' end of the fragment using terminal transferase and then to amplify using PCR. The amplicon is then to be purified by gel electrophoresis, all of which envisages that the DNA will be put back in solution. This is inconsistent with the DNA being bonded either to the glycogen or to the suggested tube.

However, to further increase the distinction already present over the '445 patent, claim 21 has now been amended to specify linkage via a covalent bond. The formation of covalent bond linkages between the nucleic acid and the carrier macromolecule is well illustrated and described in the application, including the examples.

Since the '445 patent does not teach or at a minimum suggest an immobilized nucleic acid comprising a nucleic acid bound to a carrier macromolecule having a molecular weight in excess of 80,000, which macromolecule is bound to a solid support, the applicant submits that neither a *prima facie* case of anticipation nor *prima facie* case of obviousness has been

established. In view of the foregoing, the applicant submits that the invention, as defined by claim 21, is neither anticipated by nor obvious in view of the '445 patent and therefore respectfully request that the present rejection be withdrawn.

Claims 21 and 22 were rejected 35 U.S.C. § 102(b) as allegedly being anticipated by a 1993 BioTechniques article authored by Lee *et al.* (hereinafter Lee 1993). The examiner asserted that since Lee 1993 teaches DNA sequencing using biotinylated single stranded DNA bound to beads, "the biotinylated single-strand DNAs immobilized on Dynabeads could be considered as an immobilized nucleic acid as recited in claims molecule and the bead here could be considered as a carrier macromolecule and a solid support respectively as recited in claims 21 and 22." The applicant respectfully traverses.

Yet again the applicant notes that biotin is not a macromolecule as understood in the art of molecular biology. Biotin is a C_{10} single molecule that lacks any repeating unit structure and has a molecular weight of only 224. Macromolecules are commonly defined to be "a very large molecule, such as a polymer or a protein, consisting of many smaller structural units linked together." *See* attached *American Heritage* dictionary definition (provided in the applicant's prior response). The macromolecules of required of claims 21 and 22 have a molecular weight in excess of 80,000, a molecular weight substantially greater than the molecular weight of biotin. The applicant submits that there is absolutely no basis in the general knowledge of the art for the examiner's naked and unsupported assertion that biotin constitutes a macromolecule. The examiner comments that he cannot exclude biotin from being a macromolecule on account of its molecular weight of 224 because he "cannot find the definition for macromolecule in the specification." We submit this to be irrelevant. The term macromolecule is used in the specification to have its ordinary meaning. Evidence

has been submitted as to what the meaning of the term is. The examiner has not put forward any contradicting evidence to show that the term is capable of proper use to embrace a molecular weight of 224.

Moreover, the DNA of Lee 1993 that is immobilized via biotin onto beads is not a primer, but a PCR target. The claims are directed to an immobilized nucleic acid comprising a nucleic acid bound to a carrier macromolecule having a molecular weight in excess of 80,000, which macromolecule is bound to a solid support (claim 21) and use thereof in a hybridization or amplification reaction (claim 22). Thus, in this respect, the examiner's argument for the rejection based on Lee 1993 suffers from the same deficiency as was set forth in the rejection over the '445 patent.

For the reasons given above, Lee 1993 simply fails to teach or suggest the applicant's claimed invention as defined by claims 21 and 22. In view of the forgoing, the applicant requests the withdrawal of this rejection of claims 21 and 22 over 35 U.S.C. §102(b) or in the alternative 35 U.S.C. §103(a)

The examiner rejected claims 1-6, 20, 12, 14, 15, 17, 21, and 22 under 35 U.S.C. §102(b) as allegedly being anticipated by, or in the alternative, under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 4,988,617 (hereinafter the '617 patent. It is the examiner's position that the labels described in the specification (*i.e.*, the fluorescent tag) on the oligonucleotide target probe and the adjacent oligonucleotide probe could be considered as a carrier macromolecule that did not inhibit DNA polymerase activity. The examiner also noted further that such a "tag could be considered to have a molecular weight in the range of 1,000 to 40,000,000 as recited in claim 5 since a [sic] enzyme with 10 amino acids had [sic] a

molecular weight of 1100 (average molecular weight for an amino acid is 110)." The applicant respectfully traverses.

The applicant submits that the '617 patent does not teach or suggest an immobilized nucleic acid comprising a nucleic acid bound to a carrier macromolecule having a molecular weight in excess of 80,000, which macromolecule is bound to a solid support (see claim 21) or the process for the replication of a nucleic acid template comprising bonding a primer having a sequence complementary to a portion of a nucleic acid template to a carrier macromolecule having a molecular weight in excess of 80,000; hybridizing the bound primer to said template; and extending said primer to replicate said template in complementary form (claim 1). With respect to the examiner's comments that the cited patent inherently teaches bonding a primer to a carrier macromolecule, the applicant respectfully points out to the examiner that he has provided no support for such a bold assertion. In fact and as suggested by the examiner, the cited patent discloses the use of "[an] enzyme with 10 amino acids [having] a molecular weight of 1100 (average molecular weight for an amino acid is 110)" (see page 9 of the outstanding final official action). There is no teaching to use an enzyme having a molecular weight in excess of 80,000. Therefore, the cited patent could not possibly teach or suggest the presently claimed invention.

Regarding claim 21, this requires a nucleic acid bound to a carrier macromolecule which is in turn bound to a solid support. The enzyme referred to by the examiner is bound to a nucleic acid but it is not bound to a solid support. There is no disclosure in the '617 patent of bonding the enzyme to the solid support. The enzyme cannot therefore fill the role of the carrier macromolecule of claim 21, whatever its molecular weight might be. The examiner suggests that in the '617 patent the oligonucleotide target probe or the adjacent

oligonucleotide probe labeled with a "carrier macromolecule" could be immobilized on a solid support. We respectfully point out that there is no disclosure of immobilizing an oligonucleotide via a label. Where oligonucleotides are immobilized, this is not done via the label. To do that would be pointless, since the object of the exercise under those circumstances is to see whether the ligation succeeds in joining the label to the solid support via the ligated oligonucleotides. If one of the oligonucleotides were to be immobilized to a solid support via a label (supposedly constituting a carrier macromolecule), the label would be attached to the solid support before ever the ligation was attempted, so its presence would do nothing to indicate whether the ligation occurred. This is the whole object in the '617 patent. In view of the foregoing, the applicant requests the withdrawal of the rejection under 35 U.S.C. §102(b) or in the alternative under 35 U.S.C. §103(a) over the '617 patent.

The examiner rejected claims 1, 3, 4, 6, 8, 15, and 16 and 22 under 35 U.S.C. §102(b) as allegedly being anticipated by, or in the alternative, under 35 U.S.C. §103(a) as obvious over Debre *et al.* It is the examiner's position that the fluorescent label described in the specification may be considered a carrier macromolecule. It is also the examiner's position that bonding of a primer to a carrier macromolecule is considered inherent to the cited document. The applicant respectfully traverses.

The applicant submits that the Debre *et al.* does not teach or suggest a process for the replication of a nucleic acid template comprising bonding a primer having a sequence complementary to a portion of a nucleic acid template to a carrier macromolecule having a molecular weight in excess of 80,000; hybridizing the bound primer to said template; and extending said primer to replicate said template in complementary form (claim 1). With respect to the examiner's comments that the cited patent inherently teaches bonding a primer

to a carrier macromolecule, the applicant respectfully points out to the examiner that he has, once again, provided no support for such an assertion. Debre does not identify any fluorescent label properly considered to be a carrier macromolecule, let alone one of the required molecular weight.

In view of the foregoing, the applicant requests the withdrawal of the rejection under 35 U.S.C. §102(b) or in the alternative under 35 U.S.C. §103(a) over Debre *et al.* be withdrawn.

35 U.S.C. §102(e)-35 U.S.C. §103(a)

Claims 1, 3, 4, 6, 8, 15, 18-19, and 21 were rejected 35 U.S.C. §102(e) as allegedly being anticipated by or in the alternative under 35 U.S.C. §103(a) as allegedly being obvious over U.S. Patent No. 5,652,099 (hereinafter, the '099 patent). The examiner stated that the '099 patent discloses a poly(AC) template amplified using a biotinylated synthetic 22-mer primer, and that hybridization between biotinylated poly(AC) and fluorescence labeled poly (FC) probes were detected by quenched fluorescence of the poly (FC) probe. The examiner also asserted that biotin serves as a carrier macromolecule and a detectable marker, and that hybridization between biotinylated poly(AC) probes and fluorescence labeled poly(FC) probes immobilized on avidinylated beads reads on claims 18 and 19. The applicant respectfully traverses.

The examiner continues to points to column 27 for support of this assertion of anticipation by the '099 patent. However, column 27 of the '099 patent merely teaches the use of biotinylated primers to produce amplimers having the sequence $^{5'}$BIOTIN-poly(TG)$^{3'}$. Nucleic acid probes may be mixed with these biotinylated amplimers, forming hybrids, and the hybrids may then be adsorbed via the $^{5'}$BIOTIN moiety to avidinylated beads. There is no

teaching at column 27 directed to a nucleic acid primer bound to a carrier macromoleule having a molecular weight in excess of 80,000 (claim 1), the carrier macromolecule itself being bound to a solid support (claim 21). As noted above, biotin has a molecular weight of only 224, which is not sufficient for delineating biotin as macromolecule according to this of general knowledge and skill in the art.

There is no teaching in the '099 patent of a fluorescent label that is a macromolecule. Again, with reference to the amended claims, there is no disclosure in the '099 patent to a fluorescent label having an appropriate molecular weight to satisfy the requirement for a molecular weight in excess of 80,000.

In the '099 patent, the fluorescent labels are in any case not separate from the nucleic acids, but rather take the form of modified nucleotides within the nucleic acid. It cannot properly be said therefore that there is a nucleic acid and as a separate entity a "carrier macromolecule" in the form of a fluorescent label to which the nucleic acid is bound. The modified nucleotide labels are moreover of low molecular weight as can readily be seen from their formulae, *e.g.*, in Figures 9 and 10.

Thus, the '099 patent is does not teach or suggest the claimed immobilized nucleic acid bound to a carrier macromolecule having a molecular weight in excess of 80,000, or wherein the macromolecule is itself bound to a solid support. This reference is also lacking insofar as it does not disclose a process for the replication of a nucleic acid template, the process comprising bonding a primer having a sequence complementary to a portion of a nucleic acid template to a carrier macromolecule having a molecular weight in excess of 80,000; hybridizing the bound primer to said template; and then extending said primer to replicate said template in a complementary form. The applicant respectfully submits that the

'099 patent fails to teach each and every element of the claims let alone even suggest the applicant's claimed invention, and, therefore, the rejection of this rejection of the claims under 35 U.S.C. §102(e) or in the alternative 35 U.S.C. §103(a) over this reference should be withdrawn.

III. CONCLUSION

In view of the foregoing, the claims are now believed to be in form for allowance, and such action is hereby solicited. If any point remains in issue that the examiner feels may be best resolved through a personal or telephone interview, please contact the undersigned at the telephone number indicated below.

Respectfully submitted,

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APPENDIX

MARKED UP VERSION SHOWING CHANGES MADE

IN THE CLAIMS

Claims 1, 4-8, 10, 12, 15, 16, 18, 21, and 22 were amended as follows.

1. (Twice Amended) A process for the replication of a nucleic acid template comprising:

[bonding a primer having a sequence complementary to a portion of a nucleic acid template] providing said primer being bonded to a carrier macromolecule [that does not inhibit DNA polymerase activity] having a molecular weight in excess of 80,000;

hybridizing the bound primer to said template; and

extending said primer to replicate said template in complementary form.

4. (Amended) A process as claimed in [any one of claims 1 to 3] claim 3, wherein the carrier macromolecule in its free state is substantially linear and substantially uncharged at a pH in the range of 4 to 10.

5. (Amended) A process as claimed [in any preceding claim] claim 4, wherein said carrier molecule has a peak molecular weight in the range of [1000] in excess of 80,000 to 40,000,00.

6. (Amended) A process as claimed in [any preceding] claim 5, wherein said carrier macromolecule is water soluble.

7. (Amended) A process as claimed in [any preceding] claim 6, wherein said primer is bound to said carrier macromolecule via one or more moieties derived from divinyl sulphone, each of which moieties is attached to each of the carrier macromolecule and the primer by a covalent linkage formed between on of the two vinyl groups of a divinyl sulphone molecule and a reactive functionality on the carrier macromolecule or primer.

8. (Amended) A process as claimed in [any preceding] claim 7, wherein said primer is extended by the action of polymerase incorporating nucleotides on to said primer.

10. (Amended) A process as claimed in [any of Claims 1 to 7] claim 7, wherein said primer is extended by the action of a ligase ligating said primer to at least one further primer hybridised to said template.

12. (Amended) A process as claimed in [any preceding] claim 10, wherein said carrier macromolecule is bound to a solid support.

15. (Amended) A process as claimed in [any preceding] claim 14, wherein during the extension of a said primer, a detectable marker is incorporated into the extended primer.

16. (Amended) A process as claimed in [any preceding] claim 15, wherein said extension of the primer is conducted in situ in a biological sample.

18. (Twice Amended) A method of detecting the presence of a nucleic acid bound to a carrier macromolecule comprising:

providing a first nucleic acid [bound to a carrier macromolecule that does not inhibit DNA polymerase activity] having a molecular weight in excess of 80,000;

providing a second nucleic acid [bound to a carrier macromolecule that does not inhibit DNA polymerase activity] having a molecular weight in excess of 80,000,

contacting said first and second nucleic acids under hybridization conditions, and

detecting hybridization between said first and second nucleic acids.

21. (Twice Amended) An immobilized nucleic acid comprising a nucleic acid [bound] linked via a covalent bond to a carrier macromolecule [that does not inhibit DNA polymerase activity] having a molecular weight in excess of 80,000, which macromolecule is [itself] bound to a solid support.

22. (Twice Amended) A method of using the immobilized nucleic acid as claimed in claim 21 comprising:

formulating the immobilized nucleic acid as a primer or as a hybridization probe and

introducing the immobilized nucleic acid into a hybridization or amplification reaction utilizing a primer or a hybridization probe.